# CATECHOLAMINE MODULATION OF BEHAVIOR FOLLOWING BILATERAL HIPPOCAMPAL DAMAGE

By

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To Buddy, for one.

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Abstract of Dissertation Presented to the Graduate Council of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

CATECHOLAMINE MODULATION OF BEHAVIOR FOLLOWING BILATERAL HIPPOCAMPAL DAMAGE

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This study investigated the alterations in behavior produced by pharmacologic manipulations affecting the central catecholamine systems after bilateral hippocampal damage in the rat. Various agents affecting catecholamines were administered to intact animals, to animals with hippocampal damage, and to animals with only neocortical damage, performing on several different operant schedules. High doses of amphetamine decreased responding on the fixed ratio (FR) schedule more by the animals with damage to the hippocampus than the other animals. There were no differences in the decreases in responding after the administration of norepinephrine (NE) and dopamine (DA) receptor stimulants among the groups.

Agents which blocked the synthesis of NE and DA (alpha-methyl-para-tyrosine-AMT), synthesis of NE (FLA 63) and the postsynaptic DA receptor blocking agent, haloperidol, were administered to the animals performing a differential reinforcement for low rates of responding (DRL-20) schedule and an operant brightness discrimination. Haloperidol improved the deficient DRL-20 performance of animals with hippocampal damage, and more of the drug was necessary to eliminate the

responding of the animals with hippocampal damage than other animals.

AMT and haloperidol decreased the intertrial interval (ITI) responding of the animals with damage to hippocampus performing on a simultaneous brightness discrimination task. Their deficient discrimination performance was not improved and they continued to respond more in the presence of the light that served as the stimulus for a correct response than did control animals. After haloperidol, the performance of the control animals was impaired on both the discrimination and DRL tasks. FLA 63 did not alter performance of any animals on either the DRL or the discrimination task.

These results were discussed in relationship to a functional antagonism between the hippocampus and the dopaminergic systems in the mediation of some behaviors.

# INTRODUCTION

The study of brain-behavior relationships has traditionally relied on the lesion technique in which a portion of the brain is removed and subsequent behaviors are described and quantified. The damaged area is hypothesized to be intimately involved as the "center" or the "mediator" of those behaviors which are altered following its removal. It is thought to be uninvolved in behaviors which remain intact after its removal. The major problem with these conclusions is that they rely on the assumption that the rest of the brain remains undisturbed following removal of one of its elements.

There are numerous studies that prove the above assumption to be false. These indicate that the "intact" brain areas following damage to a particular brain structure are hardly intact. Any behavioral changes which occur subsequent to brain damage may be accounted for by numerous changes which occur in the rest of the brain. Following damage of one area of the brain, many changes occur both in areas directly connected to the destroyed region and in areas remote from the destroyed area. These alterations are morphological, electrical and neurochemical in nature. Morphological changes which occur in areas denervated subsequent to brain damage include chromolytic reactions in cell bodies (Ramon Y Cajal, 1928) and alterations in dendritic branches (Westrum, White, and Ward, 1965) and spines (Rutledge, Doncan and Cant, 1972). Collateral

sprouting of axons into denervated (Moore, Björklund, and Stenevi, 1971) and intact (Schneider, 1973; Pickel, Segal and Bloom, 1974) areas have been reported. Deafferented areas become hyperexcitable (Sharpless, 1969) and supersensitive to electrical (Loser and Ward, 1967) and/or chemical (Sharpless, 1964; Ungerstedt, 1971b) stimuli. Neurochemical changes which occur are found both in areas directly associated with the damaged structure (Moore, Björklund and Stenevi, 1974) and in areas many synapses away from the damaged region (Heller, 1972). Moore et al. (1974) described increases in monoamines in the septal area following hippocampal damage. Heller (1972) suggested that decreases in telencephalic serotonin (5 HT) and norepinephrine (NE) found subsequent to medial forebrain bundle lesions were mediated across a polysynaptic system.

Since neurochemical changes have been shown to occur following brain damage and since neurotransmitter networks are intimately involved in behavior, it is valuable to look at behavioral changes induced in intact animals by neurochemical alterations. Specific neurochemical alterations can be induced by the administration of pharmacologic agents. Many of the behaviors resulting from drug administrations resemble behaviors of brain-damaged animals. They therefore provide a means for understanding brain damage and its possible concomitant neurochemical alterations. Combining the known behavioral and neurochemical actions following drug administration to normal animals with the known behavioral effects of brain damage could provide indications of the possible neurotransmitter alterations accompanying brain damage. In addition to providing

suggestions of the underlying neurochemical mechanisms involved in the behaviors following brain damage, the approach indicated here could suggest possible therapeutic interventions when brain damage impairs behavioral abilities. The administration of drugs to brain-damaged animals should also be undertaken in situations in which the animals behave similarly to normal animals. Animals with brain lesions that exhibit behavior like that of intact animals might show differences in the thresholds to drug-induced behavioral alterations or in the intensities of these alterations. Such findings would also provide information about the neurochemistry of brain damage.

One example of a close relationship between drug-induced behavioral and neurochemical changes and lesion-induced behavioral and neurochemical changes occurred in relation to the serotonergic system and pain thresholds. Administration of parachlorophenylalanine (PCPA), which inhibits tryptophan hydroxylase and thus reduces brain serotonin content, lowers the pain threshold in intact animals (Tenen, 1967). Lesions to the septal area or the dorsomedial tegmentum, as well as the medial forebrain bundle, which connects them reduce serotonin and pain thresholds. The decrease in pain thresholds following either the drug or the lesion can be increased to normal levels after administration of serotonin precursors. Even if the neurochemical consequences of this form of brain damage were unknown, the association between drug-induced chemical and behavioral changes and lesion-induced behavioral alterations would have predicted the appropriate neurochemical intervention. The PCPA-induced changes mimicked those

occurring subsequent to the lesion (Lints and Harvey, 1969). It should be recognized that the possibility of effective intervention exists only if the brain damaged area is not critical for a particular behavior.

The use of the approach outlined above for the study of the neurochemical changes accompanying brain damage requires (1) a knowledge of the behaviors which follow brain damage and (2) a knowledge of drug-induced behavioral alterations which resemble the lesion-induced behavioral alterations. This approach is particularly valuable when little is known about the neurochemical changes which occur subsequent to the brain damage. While behaviors that result from hippocampal damage have been extensively studied (see Isaacson, 1974 for a review), evidence of neurochemical changes subsequent to hippocampal damage is meager. Decreases in whole brain acetylcholine levels (Pepeu, Mulas and Mulas, 1973) and increases in septal monoamines (Moore et al., 1971) have been reported. Attempts to alleviate the behavioral deficits which follow hippocampal damage with cholinergic drugs have not proved fruitful (Van Hartesveldt, personal communication; Schneiderman and Isaacson, submitted).

Manipulations of the catecholamine transmitter systems of intact animals suggests a behavioral significance for the norepinephrine and/or dopamine (DA) systems after damage to hippocampus. For example, enhancement of catecholamine activities in intact animals often produces behaviors similar to those found after lesions of hippocampus. Amphetamine-induced premature switching in counting tasks (Laties, 1972), impairment

of the acquisition and reversal of a brightness discrimination (Beckwith, Sandman, Alexander, Gerald, and Goldman, 1974), impairment of DRL performance (Schuster and Zimmerman, 1961), increases in response for light reinforcement and resistance to extinction (Gomer and Jakubczak, 1974), increased side preferences (Glick, 1973), facilitation of active avoidance (Rech and Moore, 1968), perseverative operant responding in the absence of reward or the events usually controlling behavior (Randrup and Munkvad, 1972), increases in locomotor activity (Simpson and Iversen, 1971) and the deficient passive avoidance and prolonged extinction found subsequent to blockage of NE reuptake (Ellison, Handel, Rogers, and Weiss, 1975) resemble reports of animals with hippocampal damage (see Isaacson, 1974). On the other hand, blocking catecholamine activity in intact animals has been reported to impair active avoidance performance (Rech and Moore, 1968), decrease spontaneous activity (Rech, Borys, and Moore, 1966) and improve brightness discrimination and reversal (Saper and Sweeney, 1973).

It should be noted that not all of the behaviors studied after catecholamine enhancement resemble those found in animals with damage to hippocampus. Some findings are contrary to the apparent correlation (Kulig and Calhoun, 1972; Rahmann, 1970). However, there are many NE and DA projection systems (Ungerstedt, 1971a), only some of which may participate in the behaviors of animals after damage to the hippocampus. Yet, the fact that many of the behaviors following damage to hippocampus and following enhanced catecholamine activity do appear to be

similar suggests a role for some parts of these neurotransmitter systems in behaviors following damage to hippocampus.

Additional evidence suggests the involvement of the catecholamine systems in the behaviors that follow damage to hippocampus. Animals with damage to hippocampus have been reported to be supersensitive to the activity-inducing effects of amphetamine (Glick and Marsanico, 1974; Campbell, Ballantine and Lynch, 1971). However, the hippocampectomized animal has been reported to be less sensitive to the effects of amphetamine on a passive avoidance task (Glick, Marsanico and Greenstein, 1974) and to low doses of amphetamine on a fixed ratio task (Woodruff and Isaacson, submitted). Decreases in catecholamine functioning improve performance of rats with damage to hippocampus on a DRL-20 task (Van Hartesveldt, personal communication; Schneiderman and Isaacson, submitted; Baisden, 1973) and in passive avoidance learning (Baisden, 1973).

The present series of experiments are attempts to investigate the apparent relationship between damage to hippocampus and the catecholamine systems of the brain. Behavioral measures are assessed with the use of operant procedures. A number of studies have suggested the importance of catecholamine activity in various operant behaviors (Seiden, MacPhail and Oglesby, 1975; Sparber, 1975). Operant procedures are useful because the behaviors generated in nondrug situations usually are consistent from one study to another and from one laboratory to another. They therefore provide behavioral baselines

against which drug effects may be evaluated. Also, the methods of behavioral analysis derived from the administration of drugs to normal animals performing in operant tasks may prove useful in understanding the drug effects in brain-damaged animals. The effects of drugs have been found to be influenced by ongoing behaviors of the animals in terms of rates of responding and reinforcement densities (Seiden et al., 1975), degree of training (Singh, 1964) and stimulus control (Laties and Weiss, 1966).

The tasks selected for study are those in which animals with damage to hippocampus have been extensively studied. The fixed ratio (FR) task represents a situation in which the brain-damaged animals behave similarly to normal animals (Van Hartesveldt, 1973). Effects of amphetamine administration on this task have also been extensively studied. Most reports indicate that low doses of amphetamine will decrease FR response rates (Owen, 1960; Gibson, 1970; Sparber and Tilson, 1972; Tilson and Sparber, 1972; Woodruff and Isaacson, submitted) although a number of recent findings suggest that high doses may be necessary (Heffner, Drawbaugh and Zigmond, 1974; Brown and Seiden, 1975). Therefore, it was decided to use a wide range of doses of dl-amphetamine in this study. A comparison of the effects of amphetamine administration on the rats with damage to hippocampus and control animals performing similarly on the task might provide information about the functioning of the catecholamine systems in brain-damaged rats. The effects of the NE receptor stimulant, clonidine (Anden, Corrodi, Fuxe, Hökfelt, Rydin, and Svensson, 1970) and the DA receptor stimu-

lant, ET-495 (Corrodi, Fuxe and Ungerstedt, 1971; Corrodi, Farrebo, Fuxe, Hamberger, and Ungerstedt, 1972; Creese, 1974; Jenner and Marsden, 1975) were assessed at the conclusion of the amphetamine testing as an initial attempt to determine whether there might be differential receptor involvement in the brain-damaged and normal animals performing on the FR task.

The differential reinforcement for low rates of responding schedule (DRL) and the operant brightness discrimination task were selected for study because animals with damage to hippocampus are known to be deficient in the acquisition and performance of these problems (Clark and Isaacson, 1965; Woodruff and Isaacson, 1972). Previous administration of drugs to animals in the DRL task has indicated that decreases in catecholamine activities can improve performance of animals with damage to hippocampus, and suggests that enhanced catecholamine activity might be involved in the DRL deficit of these animals (Van Hartesveldt, personal communication; Schneiderman and Isaacson, submitted). Administration of amphetamine to normal animals disrupts their performance on the DRL task and their behavior appears to resemble that of animals with damage to the hippocampus (Schuster and Zimmerman, 1961). In the present study, agents which block synthesis of both DA and NE (alpha-methyl-para-tyrosine-AMT) (Rech et al.,1966), synthesis of NE (FLA 63) (Corrodi, Fuxe, Hamberger, and Ljungdahl, 1970a; Corrodi, Fuxe, Ljungdahl and Ogren, 1970b) or which block DA receptor sites (haloperidol) (Anden, Butcher, Corrodi, Fuxe and Ungerstedt, 1970; Kebabian, Petzold, and

Greengard, 1972; Clement-Cormier, Kebabian, Petzold, and Greengard, 1974; Iwatsubo and Clovet, 1975) were administered to animals performing on the DRL task in order to further study the involvement of the catecholamine systems in the DRL performance.

The same drugs used in the DRL task were administered to animals performing on the operant birghtness discrimination task. Administration of amphetamine to normal animals has been reported to disrupt the acquisition of a brightness discrimination (Beckwith et al., 1974). It is possible that greater than normal catecholamine activity accounts for some of the hippocampal deficits in this task. The deficits appear as both an inability to master the discrimination problem and as increased responding during the periods between cue presentations.

The DRL and the brightness discrimination problems differ in a number of aspects. For example, cues are provided in the discrimination problem while internal cues are important in the DRL task (Pellegrino and Clapp, 1971). Animals with damage to the hippocampus obtain reinforcements approximately 50 percent of the time in the discrimination task while they obtain relatively few reinforcements in the DRL problem. In both tasks, animals with damage to the hippocampus exhibit enhanced rates of responding. While these high rates of responding are inimical to good performance on the DRL schedule, their role in the discrimination deficit of animals with hippocampal damage is unknown. These task differences might result in differential drug effects.

However, if alterations in the activities of the catecholamine systems following damage to hippocampus affect some common underlying mechanism that is responsible for the performance deficits of the brain-damaged animals, manipulations of these systems by drugs might improve behaviors in a variety of different tasks. As an example of a single behavioral characteristic altered by the lesion, the brain damage might have produced an enhanced tendency toward perseverative or repetitive behaviors. Such behaviors are often ascribed to enhanced catecholaminergic functioning, and AMT and haloperidol have been reported to decrease these behaviors (Costall and Naylor, 1974a; Hollister, Breese and Cooper, 1974). Consequently, these drugs might be useful in reversing the learning difficulties of animals with damage to hippocampus.

Another "single" effect might be an effect on reactions to reward. Rewards are frequently found to have different affects on the behaviors of animals with damage to the hippocampus in comparison to control animals. For example, animals with damage to the hippocampus acquire a CRF response for a small reward faster than control animals (Van Hartesveldt, 1973) and in general, are faster to acquire a simple lever press response for reward (Schmaltz and Isaacson, 1966). When the behavioral requirements necessary to obtain reward are shifted, the animals with damage to hippocampus frequently do not modify their behaviors in accordance with the new reward contingencies (see Isaacson, 1974), but continue to respond and obtain reinforcements on a partial reinforcement basis.

These examples suggest that damage to the hippocampus may modify the activities of the catecholamine-mediated reward systems such that the systems become hyperactive. If this is directly associated with the DRL and brightness discrimination deficits of the brain-damaged animals, antagonism of those systems with the drugs used in the present study might improve performance.

## GENERAL METHODS

### Subjects

The animals employed were 61 male Long-Evans hooded rats weighing between 300 and 450 g at the time of surgery. They were housed individually in a room with a 12-hr light-dark cycle. The rats were randomly assigned to each of the experimental groups: bilateral hippocampal (plus neocortical) lesions (Group H); bilateral neocortical lesions (Group C); or unoperated controls (Group N). Each animal was used in only one behavioral study.

### Surgery

All operations were performed in one stage using clean surgical techniques. The animals were anesthetized with a 4 percent chloral hydrate solution (1cc/100 g i.p.) and placed into a stereotaxic instrument. A midline incision was made in the animal's scalp and the muscles and fascia were removed from the skull. A portion of the skull was removed with dental burr and rongeurs, exposing the neocortex lying above the hippocampus. Lesions were produced by aspiration using the procedures described previously (Isaacson and Woodruff, 1975). In Group C the neocortex was aspirated until the hippocampus became visible. For animals in Group H, the hippocampus was removed in addition to the overlying neocortex.

Following surgery, hemostasis was obtained and the scalp

was closed with 9 mm Clay Adams wound clips. The animals then received 100,000 units of Bicillin, i. m., and tetracycline was added to their water bottles for the duration of the recovery period.

The animals were allowed to recover for six to nine days after surgery and then placed on a food deprivation schedule on which they were maintained at 85 percent of their postoperative body weights. Water was available ad lib.

## Apparatus

Lehigh Valley rodent test cages (Model 143-28) equipped to dispense 45 mg food pellets, mounted in Lehigh Valley small universal isolation chambers (Model 132-02) were used. Constant illumination was provided by the houselight and a ventilation fan provided a continuous masking noise.

The operant schedules, recording of responses and presentation of reinforcement were computer controlled (Rosenberg, Woodruff, and Isaacson, 1975) for the two chambers used in the brightness discrimination study. Initially, the four operant boxes employed in the fixed ratio study were computer controlled, but technical difficulties periodically necessitated the use of standard relay programming equipment for two of the operant chambers. Relay equipment was used for two of the chambers throughout the DRL study; the other two boxes were computer controlled. The computer and relay programming equipment were located in a room adjoining the operant chambers.

Two response bars and the stimulus light above each bar in the operant box were employed in the discrimination study.

For the other two studies, one bar was retracted at all times; stimulus light cues were not used.

## Training

All training occurred postoperatively. When the animals had been reduced to 85 percent of their postoperative body weights through deprivation, barpress training was begun. Specific details of training are described in the accounts of the individual studies.

## Drugs and Injection Procedure

The drugs used included dl-amphetamine sulfate (Smith, Kline and French); clonidine (2-(2,6 dichlorophenylamino)-2-imidazoline-HCl)(Boehringer-Ingelheim); ET-495 (1-(2"-pyrimidyl)-4-piperonyl-piperazinel)(Regis Chemical Company); AMT (dl-alpha-methyl-para-tyrosine methyl ester HCl (Sigma Chemical Company); haloperidol (Haldol) (McNeil) and FLA 63 (4-methyl-1-homopiperazinylthiocarbonyl disulfide) (Regis Chemical Company).

All drugs were prepared so that the animals would receive 1 cc liquid/kg body weight. Injection solutions were prepared on the day of drug administration. Details of the drug and vehicle-control procedures are presented in the descriptions of the individual studies.

## Histology

Several of the animals died on the day after administration of FLA 63 at the conclusion of the discrimination and DRL studies. When this occurred, the brains of the operated animals were removed without perfusion. All other Group C and Group H animals were sacrificed by an overdose of chloral hydrate and

intracardially perfused with 0.9 percent saline followed by 10 percent formalin. The brains were removed, embedded in celloidin, and sectioned at 30 μ. Every eighth section was saved and stained with thionin.

## GENERAL RESULTS

### Histological Observations

Hippocampal damage was found to be extensive in all cases. In all subjects the damage involved the dorsal and lateral aspects of the structure and a variable amount of ventral hippocampus remained. The lesions frequently included damage to the fornix and the hippocampal commissure. Extra-hippocampal damage was confined to posterolateral neocortex and corpus callosum. The brain damage in Group C involved the neocortex and corpus callosum overlying dorsal, lateral and posterior hippocampus. The amount of cortical damage sustained by animals in Group C was less than that in Group H. The lesions of animals in Groups C and H were similar to those reported previously from this laboratory (Woodruff and Isaacson, 1972). Thalamic gliosis observed in all brain-damaged animals was that expected from neocortical damage (Woodruff, Baisden, and Isaacson, 1973).

When the histological preparations indicated that the brain damage of an animal did not conform to the above descriptions, the data obtained from the animal were not included in further analyses. This occurred when massive thalamic destruction was found in supposed Group H rats or when the neocortical lesion included extensive unilateral or bilateral hippocampal damage. The hippocampal damage found in some Group C animals

was never comparable to that found in Group H animals, so the animals could not be considered in either of the brain-damaged groups.

The final ns for each study were: FR study - H, 8; C, 6; N, 8; DRL study - H, 6: C, 5; N, 5; discrimination study - H, 5; C, 4; N, 5.

## EXPERIMENT I

### Fixed Ratio Schedule of Reinforcement

#### Training

Animals were shaped to barpress and allowed three FR-1 (CRF) sessions. During the next five sessions the animals were reinforced on an FR-3 schedule followed by 94 days on an FR-6 schedule. The daily FR-1, FR-3, and the first ten FR-6 sessions were 30 min in duration; FR-6 session 11 to 94 were 15 min long.

#### Injection Schedule

Responding was considered stable when the total responses made by an animal did not vary by more than 10 percent from one day to the next. This occurred for all animals after 26 days on the FR-6 schedule and subcutaneous drug injections were begun. A minimum of three days separated the injections in the dl-amphetamine series. A return to the predrug total response baseline and at least two days with 10 percent or less variation in this response measure were the criteria used to determine the day of the next drug injection. The dl-amphetamine sulphate was dissolved in physiological saline; clonidine and ET-495 were dissolved in distilled water. Pilot work determined the appropriate time to inject the drugs prior to the experimental session. The injection procedures are detailed in Table 1.

TABLE 1

FR-6 Injection Schedule

| DAY OF FR-6 | DRUG | DOSE | TIME OF INJECTION |
|---|---|---|---|
| 27 | saline | 1 cc/kg | 30-40 min presession |
| 32 | dl-amphetamine sulfate | 0.5 mg/kg | " " " |
| 38 | " | 1.0 mg/kg | " " " |
| 42 | " | 2.0 mg/kg | " " " |
| 50 | " | 2.75 mg/kg | " " " |
| 57 | " | 3.5 mg/kg | " " " |
| 62 | " | 5.0 mg/kg | " " " |
| 69 | " | 5.0 mg/kg | " " " |
| 75 | " | 2.0 mg/kg | " " " |
| 80 | saline | 1 cc/kg | " " " |
| 82 | clonidine (½ Ss-Group A) | 0.075 mg/kg | 25-30 " " |
| 82 | ET-495 (½ Ss-Group B) | 1.0 mg/kg | 5 " " |
| 89 | clonidine Group B | 0.075 mg/kg | 25-30 " " |
| 89 | ET-495 Group A | 1.0 mg/kg | 5 " " |
| 93 | Distilled HOH | 1 cc/kg | 5 " " |

Data Analysis

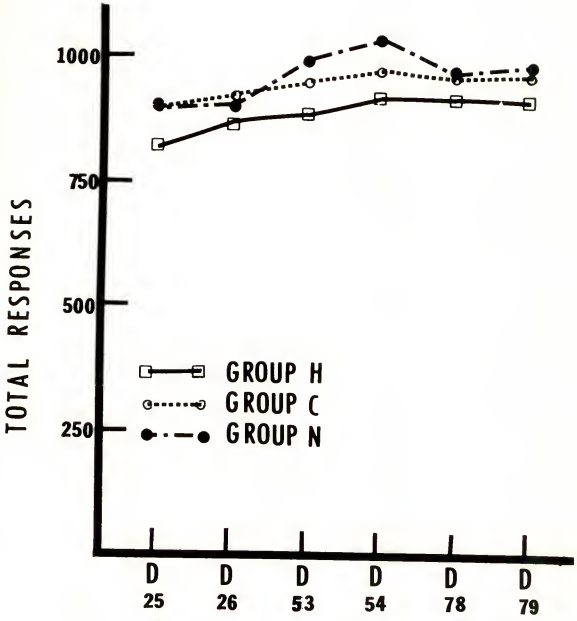
The measures analyzed included the body weights and total responses of the animals during "probe periods" which included the two control days prior to each of the saline injections (Days 25, 26, 78, 79) and a two-day nondrug period (Days 53,54) midway between the amphetamine series. Drug effects, defined as the total responses on a drug day relative to the mean of the total number of responses on the two preceding nondrug control days (percent of control responses), were compared for the different amphetamine doses and separately for the ET-495 and clonidine injections. A two-way analysis of variance for repeated measures (Winer, 1962) was followed where indicated by Duncan's multiple-range test for nearly equal ns (Bruning and Kintz, 1968) for the analysis of all data obtained prior to the ET-495 and clonidine administrations. A mixed two-way analysis of variance for repeated measures-crossover design (Cochran and Cox, 1957) was used in the analysis of the ET-495 and clonidine data. Statistical significance was accepted at $p \leq 0.05$.

Results

The analyses of body weights and total responses indicated that the experimental groups did not differ from one another at any of the "probe periods" and the "probe periods" conformed to the acceptable stability criteria (fluctuations of less than 5 percent for weight and not more than 10 percent for total responses), (Figure 1 illustrates the total responses.) The response stability criterion was maintained following injection of the vehicle solutions.

Figure 1: Mean number of responses of Groups H, C, and N during "probe periods."

D = day


TOTAL RESPONSES
1000
750
500
250
GROUP H
GROUP C
GROUP N
D 25
D 26
D 53
D 54
D 78
D 79

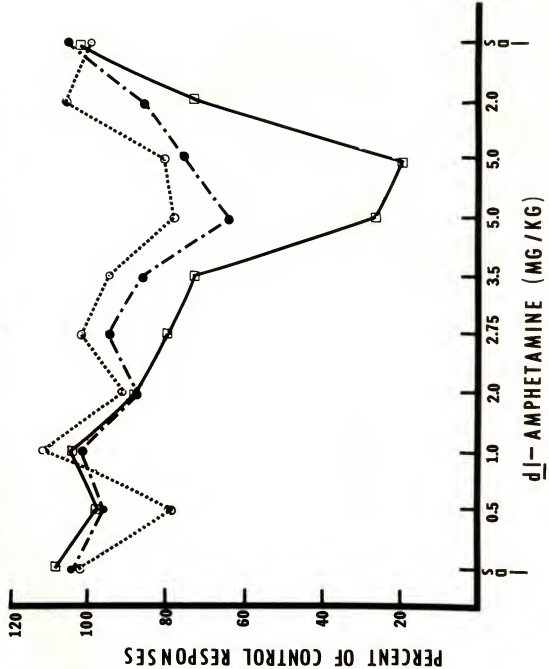
Statistical analysis of the results of the amphetamine injections yielded significant group, dose, and interaction effects. Alterations in responding following amphetamine administration were primarily response decreases. The experimental groups were differentially sensitive to the amphetamine. This was reflected by group differences in (1) the amphetamine doses which induced response alterations; (2) the magnitude of the response changes when two or more groups were affected by the same drug dose; and (3) the continued effectiveness of amphetamine with progressive increases in dosage and repeated injections of the same quantity.

Responses of Group H were altered by all doses of dl- amphetamine beyond 2.0 mg/kg (see Figure 2). The response decreases induced by the highest dose were greater than those resulting from the administration of the 2.0, 2.75, or 3.5 mg/kg doses. The effects of these smaller doses could not be differentiated from each other. Comparisons between the dose-effects in Group N indicated that responses were decreased following the 5.0 mg/kg dose of amphetamine and that the 2.0 mg/kg and 3.0 mg/kg doses were of intermediate effectiveness between the high doses and the noneffective injections. Group C dose-effect comparisons indicated that the lowest (0.5 mg/kg) and the highest (5.0 mg/kg) doses decreased responding. The effects of the second administrations of the 5.0 mg/kg and 2.0 mg/kg doses of dl-amphetamine were not significantly different from the first injections of these quantities in any of the groups.

Between-group comparisons indicated that Group H responded

Figure 2: Effects of dl-amphetamine on FR performance of Groups H, C, and N.

sal = saline


GROUP H
GROUP C
GROUP N
PERCENT OF CONTROL RESPONSES
120
100
80
60
40
20
S.D.
0.5
1.0
2.0
2.75
3.5
5.0
5.0
2.0
S.D.
d-AMPHETAMINE (MG/KG)

significantly less than Group C after the administration of the 2.75, 3.5, 5.0, and the second 2.0 mg/kg doses of dl-amphetamine and less than Group N following the highest dose. Group C differed significantly from Group N after the second 2.0 mg/kg dose. The difference between Group C and the others following the administration of 0.5 mg/kg dl-amphetamine just failed to reach the accepted level of significance.

In seven of the eight animals of Group H, it was found that once an animal started to alter responding after administration of dl-amphetamine, it was affected by all higher doses and repeated injections of the effective dose levels. A similar trend could be found for four out of eight rats in Group N but was not apparent in any of the Group C animals. (The eighth rat in Group H continued to barpress after administration of amphetamine but was observed to stop eating the acquired food pellets early in the amphetamine series and to continue to do so with increasing doses.)

Both ET-495 and clonidine decreased responding. At the doses administered, clonidine was less effective in decreasing responding than was ET-495, but the three groups did not differ in their responses to these agents.

Clonidine decreased responding 54.1 percent if administered before ET-495 and 60.3 percent if given after ET-495. ET-495 decreased responding 60.9 percent when administered prior to clonidine and 72.2 percent if given after clonidine. These results illustrate a significant order effect.

Discussion

As expected from previous reports (Van Hartesveldt, 1973), the fixed ratio (FR) schedule of reinforcement generated similar baseline rates of responding among the experimental groups. However, group differences became apparent after the administration of dl-amphetamine. Thus, the drug effects were not rate dependent, but indicate that the neurochemical mechanisms underlying performance of the task were different among the groups. The most pronounced difference occurred after the injection of the high dose of the drug. While all groups decreased responding after the administration of this dose, the decrease by Group H animals was significantly greater than that of the others.

Informal observations of the animals after administration of the high dose indicated the presence of some forms of stereotyped behaviors in all experimental groups. This suggests that the decreases in responding after the high dose might be associated with the development of stereotyped behaviors which disrupted the FR performance. It further suggests that the stereotyped behavior of animals in Group H differed from the others such that the disruption of the learned response was greater in Group H. Since increasing doses of amphetamine decrease the latency to the appearance of the peak drug effect (Taylor and Snyder, 1971) and produce more intense forms of stereotyped behavior than lower doses (Lyon and Randrup, 1972), it is possible that the latency to the appearance of, and/or the intensity of the stereotyped behavior were different in Group H compared to the others. The data of the present study

indicate that the effects of the high doses of amphetamine were intensified in animals with damage to the hippocampus relative to the control animals.

The importance of dopamine in the appearance of stereotyped behavior has been established (Randrup and Scheel-Krüger, 1966; Creese and Iversen, 1973; Snyder, 1974). There are a number of neuroanatomical loci that have been found to be involved in stereotyped behavior. These include the nigrostriatal DA system (Fog, Randrup and Parkenberg, 1970; Naylor and Olley, 1972; Creese and Iversen, 1974; Neill, Boggan and Grossman, 1974; Creese and Iversen, 1975; Iversen, Kelley, Miller and Seviour, 1975; Kelley, Seviour, and Iversen, 1975) and the mesolimbic DA structures--nucleus accumbens septi (Anden and Jackson, 1975; Ungerstedt, and Ljungberg, 1973; Costall and Naylor, 1973; Kelley et al., 1975; Costall and Naylor, 1975), olfactory tubercle (McKenzie, 1972; Costall and Naylor, 1974a; Costall and Naylor, 1975; Costall, Naylor, and Neumeyer, 1975), and nucleus amygdaloideus centralis (Costall and Naylor, 1974b; Costall and Naylor, 1975). The hypothesized intensification of stereotyped behaviors in animals after damage to hippocampus could involve any of these structures.

Increases in locomotor activity could also result in decreased bar pressing as the animals might spend more time away from the response bar. It is possible that the high doses of amphetamine resulted in greater locomotor activity in animals with damage to hippocampus compared to the others. Several reports indicate that animals with damage to hippocampus are

hyperreactive to the locomotor stimulant properties of amphetamine (Campbell et al., 1971; Glick and Marsanico, 1974). The catecholamine systems are implicated in locomotor activity although the specific neurotransmitter involved remains controversial. Various reports indicate the importance of NE (Randrup and Scheel-Krüger, 1966; Snyder, 1974), DA (Creese and Iversen, 1973; Joni and Garrattini, 1973; Thornberg and Moore, 1973; Hollister et al., 1974) or both NE and DA (Svensson, 1970; Khalsa and Davis, 1975) in the mediation of locomotor activity. With the exception of the nucleus amygdaloideus centralis, the same structures implicated in stereotyped behavior have been found to be involved in DA-induced locomotor activity (Simpson and Iversen, 1971; Pijenburg and Van Rossum, 1973; Anden and Jackson, 1975; Costall and Naylor, 1975; Creese and Iversen, 1975; Iversen et al., 1975; Kelley et al., 1975; Roberts, Zis and Fibiger, 1975). NE terminals have a widespread distribution in brain tissue (Ungerstedt, 1971a; Lindvall and Björklund, 1974) and the specific loci of the supposed NE influence on locomotor activity has not been established.

Until systematic observations are made on the behviors of the animals given high doses of dl-amphetamine, the specific behaviors and neurotransmitters associated with the significantly greater decreases in the responding of Group H are uncertain. It is possible that systems regulated by both NE and DA were involved although the observations of stereotyped behaviors after the high dose strongly suggest that this be-

havior and DA are involved. In the future, the measurements obtained in the operant task should be supplemented with formal ratings of stereotyped behavior, measures of activity and the time courses of these behaviors.

The results of the present study suggest that the differences in the neurochemical mechanisms underlying the performance of the FR schedule are presynaptic in nature. Amphetamine which acts presynaptically by releasing catecholamines and blocking reuptake (Glowinski, Axelrod, and Iversen, 1966) differentially affected the responses of the groups while the receptor stimulants ET-495 and clonidine did not. However, since only one dose of the receptor stimulants was administered, it is possible that the dose was large enough to stimulate all receptor sites and that the maximal response to the individual receptor stimulants was induced in all of the animals. Future research should assess the effect of several doses of ET-495 and clonidine in normal and brain damaged animals. Both bar press responding and observations of the behavior within the operant chamber is recommended.

Group C was the only group to decrease responding to the low dose of amphetamine which suggested that this group was more susceptible to response decreases induced by low doses of amphetamine on the FR task. Adler (1961) reported an increase in amphetamine-induced hyperactivity following posterior cortical lesions which supports one interpretation of the present findings. Since low doses of amphetamine preferentially affect NE (Azzaro and Rutledge, 1973) and NE has been implicated in

activity, the present study might suggest that the animals with neocortical damage were more sensitive to NE-induced increases in activity. However, it is difficult to explain the finding that Group C did not show responsiveness to amphetamine again until the high dose was given. This presents difficulties in determining threshold doses for this group. This same problem is found in Group N since this group did not show consistent response effects with increasing doses of amphetamine. Actually, only Group H exhibited consistency in the response-decreasing effects of amphetamine. Group H decreased responding after the administration of all doses ranging from 2.0 to 5.0 mg/kg dl- amphetamine. A consistency in response decreases was also apparent in the reactions of the individual animals of this group. One possible explanation for these results is that redundant neurochemical systems in Groups C and N are capable of taking over behavioral functioning when a system that is usually involved is compromised by the administration of a drug agent. Thus, the potential disruption of operant responding by amphetamine actions on the catecholamine systems could be overridden by the operations of other neurotransmitter systems. The data indicates that this is more likely in Group C than in Group N. Removal of the hippocampus, in addition to the neocortex, does not allow for the above possibility. This suggests that the behavior of Group H is dominated by the catecholamine systems either because these systems are relatively enhanced after damage to hippocampus and/or because other systems which can "take over" the operant behavior are eliminated or deemphasized.

## EXPERIMENT II

### DRL Schedule of Reinforcement

#### Training

Subjects were first shaped to barpress and given six to eight daily nine-min sessions on a continuous reinforcement (CRF) schedule. When the rats were responding consistently on the CRF schedule, they were directly switched to the DRL-20 schedule in which they were required to wait at least 20 sec between barpresses in order to obtain a reinforcement. Responses prior to this 20-sec interval reset the system so that the animal had to wait another 20 sec before a response would produce a reinforcement. DRL sessions were 30 min long and were continued for 63 days.

#### Injection Schedule

After the animals had been performing on the DRL-20 schedule for 21 days, the number of reinforcements obtained by the animals of Groups C and N did not vary by more than 15 percent from day to day. The animals with hippocampal damage were less stable because the number of reinforcements they obtained was so few (between 5 and 10 per session); a change of two or three reinforcements in a session produced a larger percentage change than in Groups C and N. On Day 22, drug injections were begun. Seven days separated the administration of the different drugs (AMT, haloperidol, FLA 63).

AMT was first administered subcutaneously and was followed four days later by intraperitoneal injections. All other injections were given via the subcutaneous route. If a drug altered DRL performance, the next injection was not given until the animals were receiving approximately the same number of reinforcements as they were obtaining prior to the drug.

The vehicle-control procedures for AMT consisted of three paired injections of 0.9 percent saline and dextrose in saline (1 cc/injection)given 4 hr apart. The dextrose in saline was administered to reduce possible renal damage. Injections of AMT dissolved in saline were given according to this same schedule following procedures which should have resulted in maximal catecholamine depletion at the time of the experimental session (Rech et al., 1966). Haloperidol was dissolved in a 1 percent lactic acid solution and adjusted to the appropriate dosage with distilled water. A 0.01 mg/kg dose of haloperidol was considered to be the vehicle-control substance since it was found to be ineffective in altering operant behavior (previous data, see also Experiment III). Previous data indicated the appropriate amount of time between haloperidol injection and the experimental session. FLA 63 was suspended in a 1 percent gum tragacanth solution. Previous reports of the procedures necessary to produce substantial and selective NE depletion by FLA 63 were used to determine the amount of time between injection and behavioral testing (Corrodi et al., 1970a). Table 2 presents details of the drug administrations.

TABLE 2

DRL Injection Schedule

| DAYS of TRAINING | DRUG | DOSE | TIME of INJECTION |
|---|---|---|---|
| 22 | saline | 1 cc/kg | 12, 8, and 4 hr presession |
| 22 | dextrose in saline | 1 cc | 12, 8, and 4 hr presession |
| 27 | AMT | 50 mg/kg | 12, 8, and 4 hr presession |
| 27 | dextrose in saline | 1 cc | 12, 8, and 4 hr presession |
| 31 | AMT | 50 mg/kg | 12, 8, and 4 hr presession |
| 31 | dextrose in saline | 1 cc | 12, 8, and 4 hr presession |
| 39 | haloperidol | 0.01 mg/kg | 20 min presession |
| 42 | haloperidol | 0.025 mg/kg | 20 min presession |
| 45 | haloperidol | 0.04 mg/kg | 20 min presession |
| 48 | haloperidol | 0.08 mg/kg | 20 min presession |
| 51 | haloperidol | 0.08 mg/kg | 20 min presession |
| 54 | haloperidol | 0.025 mg/kg | 20 min presession |
| 59 | 1% gum tragacanth | 1 cc/kg | 4 hr presession |
| 62 | FLA 63 | 10 mg/kg | 4 hr presession |

Data Analysis

The total number of responses emitted and the number of reinforcements obtained were subjected to a two-way analysis of variance for repeated measures on one factor (Winer, 1962), followed where indicated by Duncan's multiple-range test for nearly equal ns (Bruning and Kintz, 1968). Included in the analyses were the scores from the three nondrug sessions prior to the first injection, the scores from each drug day, and the scores from the nondrug session immediately preceding each drug day. Statistical significance was defined as $p \leq 0.05$.

The time between successive barpresses (interresponse time or IRT) was analyzed by tabulation of the responses occurring in each of five 4-sec bins from 0 to 19.99 sec. Responses occurring 20 sec or longer after a previous response went into a sixth bin. Responses in each bin were converted into a percentage of the total responses of each session.

Results

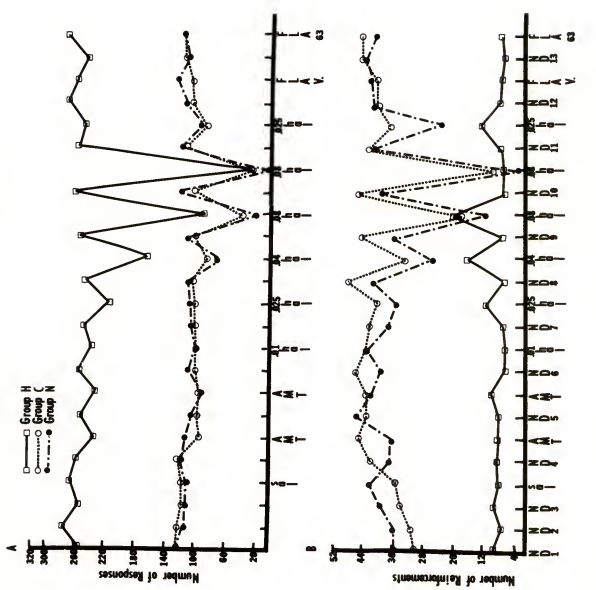
The analyses of variance resulted in significant group, days and interaction effects for the number of reinforcements and the number of responses. Further analysis revealed that on all nondrug (ND) days, Group H responded significantly more and received significantly fewer reinforcements than Groups C or N. Groups C and N did not differ in the number of responses emitted on any nondrug days and, with the exception of ND 9, did not significantly differ in the number of reinforcements obtained over the course of the nondrug days analyzed, (see Figures 3A and 3B). Within-group

Figure 3A: Mean number of responses of Groups H, C, and N on relevant drug and nondrug sessions of the DRL-20 task.

ND = nondrug session;
sal = saline; hal = haloperidol-dose in mg/kg;
FLA V. = FLA 63 vehicle.

Figure 3B: Mean number of reinforcements obtained by Groups H, C, and N on relevant drug and nondrug sessions of the DRL-20 task.

ND = nondrug session;
sal = saline; hal = haloperidol-dose in mg/kg;
FLA V. = FLA 63 vehicle.


A
Group H
Group C
Group N
Number of Responses
B
Number of Reinforcements

analysis of the nondrug days indicated that Group C obtained fewer reinforcements on the 3 days of training immediately preceding the saline vehicle injection than on any of the subsequent nondrug days. The other groups maintained the number of reinforcements obtained over the course of the nondrug days anaylzed. Number of responses did not significantly differ across the nondrug days for any of the three groups.

Haloperidol was the only agent found to alter the DRL measures and it did so in all groups. Group H decreased responding when administered 0.04 mg/kg, and continued to decrease after the two 0.08 mg/kg doses. After the injection of 0.04 mg/kg and the first 0.08 mg/kg doses of haloperidol, the decreased responding was accompanied by increases in the number of reinforcements obtained. Groups N and C progressively decreased the number of reinforcements obtained when administered the 0.04 mg/kg and 0.08 mg/kg doses of haloperidol. Group N also decreased the number of obtained reinforcements after the second administration of 0.025 mg/kg haloperidol. The reinforcement decreases in Groups C and N were accompanied by significant response decreases only after the high dose.

Between-group differences were altered after the high dose of haloperidol and following the second 0.025 mg/kg injection. After the first 0.08 mg/kg dose, the normal animals received significantly fewer reinforcements than Group H while Group C did not differ significantly from Groups N and H on this measure. Group H responded more than Group N after this dose while Group C did not differ significantly from either

Group N or H. Group differences in the number of reinforcements obtained and the number of responses emitted were not found after the second 0.08 mg/kg dose. The decrease in reinforcements obtained by Group N after the second administration of 0.025 mg/kg haloperidol resulted in this group receiving significantly fewer reinforcements than Group C but still more than Group H.

When haloperidol altered DRL performance, IRT distributions were examined only when the animals continued to respond. After both administrations of the high dose to Groups C and N and after the second administration of the high dose to Group H, a majority of the animals stopped responding or responded so infrequently that grouped IRT distributions were not considered. The decrease in the number of reinforcements obtained by Groups C and N when responding was not significantly altered indicates a change in the temporal patterning of their responses. Group IRT distributions suggest that minor alterations in the response patterns accounted for decreases in the number of reinforcements obtained after 0.04 mg/kg haloperidol (see Figures 4A and 4B). In comparison to the ineffective 0.01 mg/kg haloperidol dose, Group C showed an increased tendency to emit responses separated by 4 sec and by 12 to 16 sec when administered 0.04 mg/kg haloperidol. At this same dose, Group N showed an increased tendency to respond after waiting 4 to 12 sec accompanied by decreases in the proportion of responses separated by more than 12 sec. More pronounced changes in the temporal patterning were found

after administration of the second 0.025 mg/kg dose to Group N. These include increases in responses separated by less than 12 sec and decreases in those separated by more than 12 sec (see Figure 4A).

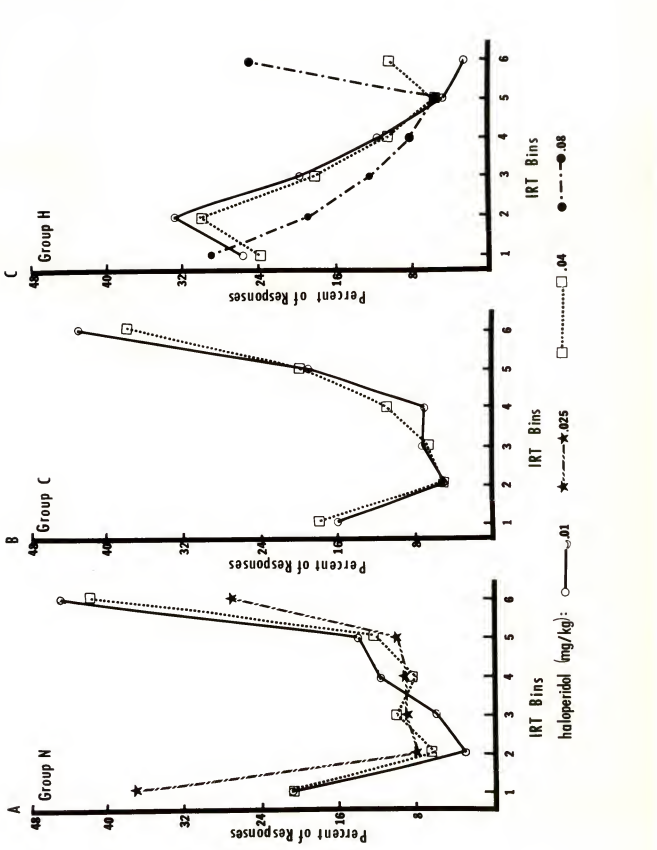
Group H received significantly more reinforcements after 0.04 mg/kg and the first 0.08 mg/kg haloperidol than on any other experimental days. When compared to 0.01 mg/kg haloperidol, their pattern of responding at 0.04 mg/kg indicated an increased proportion of responses separated by more than 20 sec in addition to decreases at all other interresponse times with the exception of responses separated by 12 to 19.99 sec (see Figure 4C). After the first 0.08 mg/kg haloperidol dose, responses separated by less than 4 sec and greater than 20 sec were increased while those separated by 4-16 sec were decreased (see Figure 4C). Since 66 percent of Group H animals were responding less than 20 times during the entire session following the second administration of 0.08 mg/kg haloperidol, continued reinforcement increases were not found and IRT distributions were not considered.

The number of responses occurring during each successive 5 min of the 30 min DRL session were tabulated. When the drugs altered the number of responses it was possible to roughly approximate the time of onset of the drug effects by comparing the 5-min response distributions during the nondrug and vehicle days to the distribution on the drug days. In all groups the 0.08 mg/kg dose of haloperidol decreased responding

Figure 4A: Interresponse time (IRT) distributions of Group N on DRL-20 sessions after administration of haloperidol.

Figure 4B: Interresponse time (IRT) distributions of Group C on DRL-20 sessions after administration of haloperidol.

Figure 4C: Interresponse time (IRT) distributions of Group H on DRL-20 sessions after administration of haloperidol.


A
Group N
B
Group C
C
Group H
Percent of Responses
IRT Bins
haloperidol (mg/kg): .01 .025 .04 .08

within the first 5-min period. After the first administration of the high dose, only Group H consistently responded throughout the 30-min session and decreases in responding were found to occur throughout the session. A consistent pattern of the latency to and duration of response decreases by Group H after 0.04 mg/kg haloperidol could not be detected from the available data.

Behavioral alterations in DRL performance were not found at the time of the supposed NE depletions induced by FLA 63. However, the drug resulted in toxic manifestations in most of the animals and death to three of the rats on the day after the supposed central NE decreases.

Observations

On vehicle and drug injection days 2-min observations of the rats' behavior were made 15 min after the animals were placed in the operant chamber. Observations were made of the behavior of the animals when they were directly manipulating the response lever and the activities between lever manipulations, "interresponse periods."

Following the administration of the vehicle agents, Groups C and N would typically chew on the floor bars and move backwards during the "interresponse periods." At these times, Group H animals would run around the chamber. "Interresponse" activities were altered following the administration of several of the haloperidol doses. Typical betweenbarpress activities of all groups decreased after injection

of 0.04 mg/kg haloperidol. After the first administration of 0.08 mg/kg haloperidol, Group H animals were observed to repetitively move their heads from the bar to the foodwell during "interresponse periods." This latter behavior was also observed after administration of the second high dose. Groups C and N decreased all of their activities when administered the 0.08 mg/kg doses of haloperidol. The nondrug pattern of activities was seen after the second 0.025 mg/kg dose was administered to Groups C and H. The floor bar chewing and backward locomotion were not observed in Group N.

On completion of the haloperidol sessions, the rats were tested for catalepsy using a spool test (Aspen, Boggiolini, Burshi, Ruch, and Stille, 1973) and the latency to front paw withdrawal was recorded. The reaction of the rats to the rat chow placed in their home cages at the conclusion of the experimental sessions and the general behaviors of the animals before and after the sessions were noted.

Cataleptic responses were never found in any of the rats. All animals responded as usual to the food pellets placed in their home cages. General behaviors outside of the operant chamber were not different on drug or vehicle days.

Discussion

As previously reported (Clark and Isaacson, 1965) animals with damage to the hippocampus were imparied in their performance of the DRL-20 schedule of reinforcement. In com-

parison to control animals, animals in Group H responded more and received fewer reinforcements. Group H's interresponse time (IRT) distribution, which reflects the temporal patterning of the animals' responses, indicated that the predominant proportion of responses were separated by short time intervals. During the interresponse periods, the animals with damage to hippocampus characteristically ran around the operant chamber.

The administration of the DA blocker, haloperidol, affected the performance of the DRL schedule of reinforcement in all of the experimental groups. However, the drug affected the measures of DRL performance at different thresholds and in different ways in the experimental groups. The administration of several doses of haloperidol improved the DRL performance of animals with damage to the hippocampus. Their usual mode of performance was replaced by decreases in the number of responses emitted and increases in the number of reinforcements obtained. Haloperidol administration also altered the temporal patterning of their responses. The threshold dose necessary to alter the behavior (0.04 mg/kg) resulted in modifications in the temporal patterning; relative to the IRT distribution following the vehicle injection, short IRTs decreased and longer IRTs increased. After the administration of the next dose in the haloperidol series (0.08 mg/kg) the IRT distribution indicated that the animals with hippocampal lesions were increasing the proportions of responses separated by both the shortest and the longest time intervals; they were also de-

creasing responses separated by intermediate time periods. This bimodal IRT distribution in which the highest proportions of responses have the shortest and the longest IRTs, is one of the characteristics of the response distribution of normal animals. Although the interresponse running activity of the animals with damage to hippocampus was observed to decrease in frequency after the 0.04 mg/kg dose of haloperidol, it was only after the administration of the high dose that a novel and consistent interresponse behavior was seen--the repetitive movements of the animals' heads between the food receptacle and the response bar.

Although the absolute number of reinforcements obtained by Group H after the administration of the first high dose of haloperidol was not significantly greater than the number obtained after the threshold dose which altered DRL performance, several factors suggest that the DRL performance was further improved by the high dose. These include the findings that (1) the number of nonreinforced responses was further decreased relative to the threshold dose, (2) the IRT distribution exhibited some "normal" characteristics, and (3) a new "interresponse" activity developed (repetitive head movement) which possibly functioned as a "mediating" behavior used in timing the required DRL intervals.

However, continued administration of haloperidol did not result in continued improvements in the DRL performance of the animals in Group H. After the second administration of the

high dose, responding was eliminated in 66 percent of Group H animals. This was probably due to cumulative drug effects. Interestingly, the novel type of "interresponse activity" seen after the administration of the first high dose persisted despite the fact that the animals stopped pressing the bar.

The administration of haloperidol to the animals in Groups C and N resulted in several performance effects that were different from those induced in Group H. The dose that first affected DRL performance was the same as the threshold dose in Group H (0.04 mg/kg). However, relative to nondrug days, Groups C and N significantly decreased the number of reinforcements that they obtained without significantly altering their response output. This indicates that under haloperidol, these animals were emitting relatively more unreinforced responses and less reinforced responses than on nondrug days; i.e., their DRL performance was impaired. In addition to effects on responses and reinforcements, slight modifications in the temporal patterning of responses and elimination of the interresponse activities indicate that the threshold dose of haloperidol disrupted the usual mode of DRL performance in Groups C and N.

The high dose of haloperidol decreased both the total responses and the number of reinforcements obtained by the control animals. After the first administration of the high dose, a majority of the rats stopped responding or responded so infrequently as to make evaluation of grouped DRL performance impractical. When it was possible to observe further changes, the second high dose resulted in continued response and rein-

forcement decreases.

Group N was the only group affected by the second administration of the 0.025 mg/kg dose of haloperidol. The effects found were similar to those that occurred after the administration of the first dose of the drug that altered DRL performance (0.04 mg/kg); the number of reinforcements obtained were decreased while the number of responses made were unaffected. Between-barpress behaviors were eliminated. At this time, the temporal patterning was more disrupted than after the first effective haloperidol dose; particularly large increases in the shortest and decreases in the longest IRTs were found. The reason for the selective and somewhat enhanced effect of the second 0.025 mg/kg dose on Group N is not clear, but may be due to cumulative drug effects and suggests that Groups C and H are less susceptible to these cumulative effects than is Group N.

Administration of doses of haloperidol which do not eliminate responding appear to interact with and to disrupt what the animals are doing or how they are performing the task on nondrug days. The results from the present study in combination with other reports of the behavioral affects of drug administrations to animals performing on a DRL schedule of reinforcement suggest that some systems critical for DRL performance may be regulated by the catecholamines. These systems require some optimal catecholaminergic activity and any deviations from the optimum are detrimental to task performance. The administration of haloperidol, in the present study, could improve the relatively poor DRL performance of the animals with

damage to the hippocampus and impair the relatively good performance of the control animals. The neuroleptic, chlorpromazine, which has anticatecholaminergic properties, was previously found to have opposite effects on good and poor DRL performances, impairing the former and improving the latter (Schneiderman and Isaacson, submitted). Increases in catecholamine activities after the administration of amphetamine have been found to alter performance of the DRL schedule by normal animals such that it resembles the behavior of animals with damage to the hippocampus. These findings suggest that increased activity of the catecholamine systems involved in efficient DRL performance--perhaps DA systems in particular--results in some of the DRL deficit of Group H. It might be possible to devise some type of long-term drug administration schedule to produce continuous improvements in the animals with damage to the hippocampus. If haloperidol is to be used, such a regimen must take into account the effects of the drug on responding, per se.

The data of the present study indicates that increasing doses (or cumulative effects of a progressive series of doses) of haloperidol lead to an elimination of responding, per se. The mechanism(s) involved in this phenomenon might include effects on the ability to respond, the motivation to respond, or the significance of the stimuli or rewards associated with the processes of the DRL task. The tests for catalepsy, the reactions of the animals to food given to them in their home cages and the general "normal" behaviors of the animals outside

of the operant chamber suggest that the elimination of responding is specifically associated with performance of the DRL schedule.

The threshold for elimination of responding by haloperidol is lowest in the control animals. Although it takes more haloperidol administrations to eliminate responding in Group H, the high numbers of unreinforced responses which typify the mode of DRL performance of this group are initially more susceptible to decreases by haloperidol than are the responses of the control animals, as indicated by the fact that the first dose of haloperidol found to affect DRL performance selectively decreases responses in Group H compared to the control animals. It is possible that haloperidol initially interacts with a mechanism responsible for high rates of unreinforced responses typical of Group H prior to acting on a mechanism responsible for decreasing responding, per se. In control animals, the typical mode of appropriate DRL performance is also disrupted prior to drug effects on the mechanism involved in responding, per se. However, low predrug response rates of Groups C and N may account for the earlier disruption by haloperidol of the mechanism associated with responding, per se, in these animals compared to Group H. The present study indicates that more DA blockage is necessary to disrupt the typical mode of Group H responding than the mode of Group C and Group N responding prior to affecting a mechanism responsible for this elimination of responding, per se, and suggests that the activity of some system regulated by DA is increased

after damage to the hippocampus and this is associated with the higher response rate of animals with damage to the hippocampus in comparison to control animals.

The administration of the catecholamine synthesis blocker, AMT, did not result in any measuralbe behavioral effects on the DRL-20 schedule of reinforcement. There are several possible explanations for these findings. Numerous reports suggest that the reliability of AMT in producing behavioral alterations is questionable. While there are studies indicating major behavioral effects after AMT (Moore, 1966; Rech et al., 1966; Pirch and Rech, 1968a; Schoenfeld and Seiden, 1969; Saper and Sweeney, 1973) there are reports to the contrary (Weissman and Koe, 1965; Corrodi and Hanson, 1966; Seiden et al., 1975). Factors such as the duration of isolation of the animals prior to the drug administration (Pirch and Rech, 1968a; 1968b), type of task (Weissman and Koe, 1965; Moore, 1966; Corrodi and Hanson, 1966; Rech et al., 1966) and individual animal susceptibility (Corrodi and Hanson, 1966) are found to influence the behavioral effect of AMT. Differences in the drug's effects are often dependent on the apparatus used to study a particular behavior. For example, conditioned avoidance in an operant chamber is more affected than is conditioned shuttle box avoidance (Corrodi and Hanson, 1966) which is more influenced by the drug than is a "jump out" discriminated avoidance (Weissman and Koe, 1965). Thus, numerous factors appear to determine whether or not behavioral alterations will accompany the administration of AMT. The reasons why AMT was previously found to alter DRL-20 performance (Schneiderman and Isaacson,

submitted) in contrast to the present study are not clear. Since several procedural differences exist any one or a combination of these could account for the contrary findings. In addition, the baseline behavior of the animals at the time of administration of the drug in the two studies was not equated; different baseline rates of responding could contribute to different drug effects. The failure to find effects of AMT in the present study is similar to that reported with the use of a DRL-17.5 sec schedule of reinforcement (Seiden et al., 1975).

A second possibility for lack of effects is that the synthesis of the catecholamines in the present study was not sufficiently blocked after AMT administration to result in observable behavioral alterations. If catecholamine depletion was not complete, there may have been enough of the neurotransmitters available for performance of the task. It has been reported that large and frequent doses of AMT are necessary to ensure synthesis blockade (Kizer, Kopin and Zavin, 1975) and that in areas that are rich in catecholamines, very large doses never result in complete depletion of nerve terminal catecholamines (Anden, Corrodi, Dahlström, Fuxe and Hökfelt, 1966). It has been suggested that the nonfunctional "reserve" pool of catecholamines can become functional after AMT administration such that behaviors may be sustanied (Rech and Moore, 1968; Franklin and Herberg, 1974).

DRL performance alterations were not found at the time of the supposed central effects of the NE synthesis inhibitor,

FLA 63, and it is possible that a selective blockade of DA is necessary to produce behavioral alterations. However, the behavioral effects subsequent to NE synthesis inhibition appear to be task specific. Conditioned avoidance behavior (Moore and Rech, 1969; Hurwitz, Robinson and Barofsky, 1971) and shock-induced aggression (Thoa, Eichelman and Ng, 1972) are unaffected while motor activity is depressed (Svensson and Waldeck, 1969; Thornberg and Moore, 1971) after inhibition of NE synthesis. It has also been reported that the decrease in NE concentration following FLA 63 is not correlated with motor activity and that repeated injections are necessary to produce decreases in activity (Corrodi et al., 1970a). Performance of the DRL schedule of reinforcement might be another example of a task that is unaffected by NE depletion. On the other hand, incomplete synthesis inhibition or mobilization of "reserve" pools are possible explanations for the lack of behavioral alterations found at the time of supposed maximal effect of FLA 63 on central NE.

It therefore appears that synthesis inhibitors may not be as reliable as receptor blockers in affecting some behaviors. Subtle factors seem to be involved in the effects of the synthesis inhibitors. Future research should employ receptor blockers. If synthesis inhibitors are used, biochemical determinations of their effects on the neurotransmitter systems in animals performing specific tasks should be determined.

The animals became extremely ill on the day following the administration of FLA 63. They had obvious respiratory and thermoregulatory problems; severe sedation and piloerection

were also manifested. DRL performance was affected at this time. The FLA 63 proved lethal to several of the animals and others required from two to five days before DRL performance was restabilized. While FLA 63 has previously been reported to be both toxic and lethal (Corrodi et al., 1970a), the doses employed were higher than that used in the present experiment. Perhaps the prolonged food deprivation schedule or the administration of other drug agents prior to the FLA 63 injection contributed to the enhanced toxicity of the agent. Doses up to 25 mg/kg administered to food deprived pilot animals were not toxic or lethal. However, these pilot animals were not performing in the operant tasks nor had they been administered any drugs prior to the FLA 63 injection. In addition, the degree of deprivation of the pilot animals was not necessarily directly equated to that of the rats performing on the DRL schedule.

## EXPERIMENT III

### Brightness Discrimination Study

#### Training

The animals were first trained on a continuous reinforcement (CRF) schedule. Subjects were given 6 to 7 30-min CRF sessions, at the end of which all subjects were responding to both bars in the operant chamber. Following barpress training, the animals were directly switched to the visual discrimination task. The discrimination paradigm was programmed such that at the beginning of each trial a stimulus light ($S_D$) was illuminated over the bar to which a response would be reinforced. The light stimulus was terminated by a response or a period of 5 sec without a response. Following a correct response or a "no response" the position of $S_D$ was randomly determined. If the subject made an incorrect response, the $S_D$ remained over the same bar on subsequent trials until a correct response or a "no response" was made. Consequently, "errors of commission" were subject to a correction procedure while nonresponding or "errors of omission" were not. Following termination of $S_D$ a 10-15 sec intertrial interval (ITI) ensued. During the ITI the cue light was off but the houselight remained on; levers were not retracted. The daily testing sessions were 30 min in length and contained between 90 and 120 trials. Training continued for 102 days.

Injection Schedule

After 34 days of visual discrimination training, the performance of the individual animals had stabilized in that the percent of responses made in the presence of the $S_D$ and the percent correct response scores did not vary by more than 10 percent from one day to the next. At this time, subcutaneous drug injections were begun. At least nine days separated the administration of the different drugs (AMT,haloperidol, and FLA 63). Within the haloperidol series, a criterion of 2 days of performance at predrug levels (as measured by percent correct and responding in the presence of the $S_D$) had to be met before the initial administration of each dose. The number of days required to reach the criterion for the first dose was used as the number of nondrug days before the second administration of that dose.

The vehicle for AMT consisted of three paired injections of 0.9 percent saline and dextrose in saline given 4 hr apart. The dextrose in saline was administered to reduce possible renal damage. Injections of AMT dissolved in saline were given according to this same schedule following procedures which should have resulted in maximal catecholamine depletion at the time of the experimental session (Rech et al., 1966). A 1 percent lactic acid solution was the vehicle injection for haloperidol. Haloperidol was first dissolved in this solution and adjusted to the appropriate dosage with distilled water. Pilot work determined the appropriate amount of time between the drug injection and the experimental session. The FLA 63 was suspended in a 1 percent gum tragacanth solution. The amount of

time between injection of FLA 63 and the experimental session was in accordance with procedures which produced substantial and selective NE depletion (Corrodi et al., 1970a). All injections were given subcutaneously. Table 3 presents details of the drug administrations.

Data Analysis

The discrimination measures analyzed include the percent of responses in the presence of the stimulus light (number of responses in the presence of $S_D$/number of light presentations), the percent of correct responses relative to the number of responses to the light (number of reinforcements/number of responses to the light stimulus), and the average number of intertrial interval responses in the first 5 sec of ten intertrial intervals [(number of ITI responses in the first 5 sec of all ITI periods/total number of ITI periods) x 10].

Two-way analyses of variance for repeated measures on one factor (Winer, 1962), followed where appropriate by Duncan's multiple-range test for nearly equal ns (Bruning and Kintz, 1968), were used in analyzing the data for each of the discrimination measures. Included in the analyses were the scores from two days immediately preceeding any injection (D 33 and D 34), the injection days, and the average of the scores for the two nondrug (ND) days prior to each drug administration (ND 1-13). The scores obtained on the two days prior to drug injection did not fluctuate by more than 10 percent. Statistical significance was accepted at the $p \leq 0.05$ level.

Results

The analyses of variance indicated significant group,

TABLE 3

Brightness Discrimination Injection Schedule

| DAYS of TRAINING | DRUG | DOSE | TIME of INJECTION |
|---|---|---|---|
| 35 | saline | 1 cc/kg | 12, 8, and 4 hr presession |
| 35 | dextrose in saline | 1 cc | " " " " |
| 38 | AMT | 50 mg/kg | " " " " |
| 38 | dextrose in saline | 1 cc | " " " " |
| 44 | 1% lactic acid | 1 cc/kg | 20 min presession |
| 48 | haloperidol | 0.08 mg/kg | " " " |
| 54 | haloperidol | 0.04 mg/kg | " " " |
| 59 | haloperidol | 0.01 mg/kg | " " " |
| 63 | haloperidol | 0.025 mg/kg | " " " |
| 68 | haloperidol | 0.01 mg/kg | " " " |
| 72 | haloperidol | 0.025 mg/kg | " " " |
| 77 | haloperidol | 0.04 mg/kg | " " " |
| 82 | haloperidol | 0.08 mg/kg | " " " |
| 88 | 1% lactic acid | 1 cc/kg | 4 hr presession |
| 96 | 1% gum tragacanth | 1 cc/kg | " " " |
| 101 | FLA 63 | 25 mg/kg | " " " |

days and interaction effects for each of the discrimination measures.

Percent of responding during $S_D$ periods. Groups H, C, and N did not differ in the percent of responding during the periods of presentation of the stimulus light on any of the nondrug days or on any of the four vehicle injection days. Haloperidol was the only drug to alter the responses made to $S_D$. Figures 5, 6, and 7 indicate that 0.025, 0.04, and 0.08 mg/kg doses of haloperidol significantly decreased responding by the three groups; the 0.01 mg/kg dose did not alter responding. After the administration of all effective doses (with the exception of the first haloperidol injection at the 0.08 mg/kg dose) $S_D$ responding by Group H was decreased less than was responding by Groups C and N. (After administration of the first 0.08 mg/kg dose, the difference between Groups H and N just failed to reach the acceptable level of significance.) The lessened effect on Group H was particularly evident after the second administrations of 0.025 mg/kg and 0.04 mg/kg haloperidol when the only group differences are between Group H and the others.

Comparison of the first descending series of haloperidol doses indicated that within each group response decreases were not significantly changed following administration of the highest doses (0.08 mg/kg and 0.04 mg/kg). These doses were more effective in reducing responding by Groups H and N than was the 0.025 mg/kg dose. Response decreases by Group C were not significantly different from one another under these three effective doses. During the second ascending series, dose-effect

Figure 5: Mean percent of responses during $S_D$ in the brightness discrimination task.

D = day; sal = saline; ND = nondrug session; hal V. = haloperidol vehicle; hal = haloperidol-dose in mg/kg; FLA V. = FLA 63 vehicle.

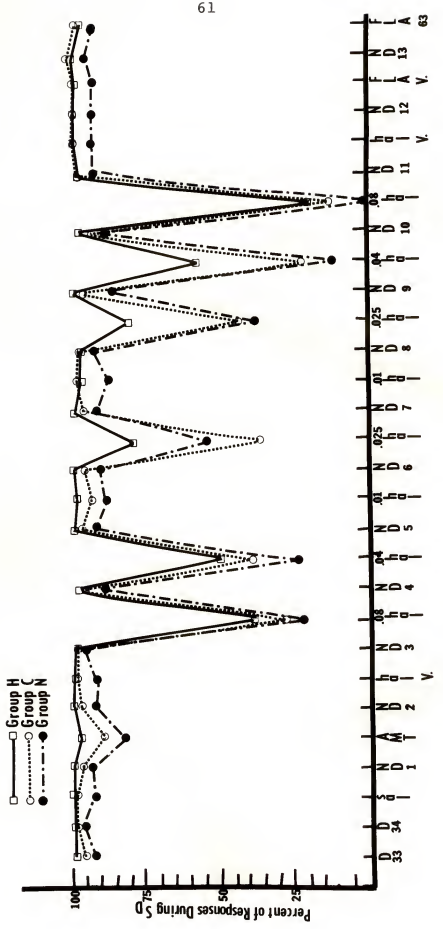

Group H
Group C
Group N
Percent of Responses During S D
100
75
50
25
D 33
D 34
S — 1
N D — 2
A — 3
N D — 4
N D — 5
N D — 6
N D — 7
N D — 8
N D — 9
N D — 10
N D — 11
N D — 12
F N D — 13
A — 63
V.
.08
.04
.025
.01
.025
.01
.08
.04

Figure 6: Changes in the percent of responses during $S_D$ after drug administrations.

hal = haloperidol-dose in mg/kg.
Center chart represents alterations within each group--filled circles = no change; arrows = decrease in responding. Side figures indicate between group differences after drug administrations. C = Group C; H = Group H; N = Group N. Intersection of Groups on grids adjacent to drugs indicates significant (star) or nonsignificant (open circle) group differences.

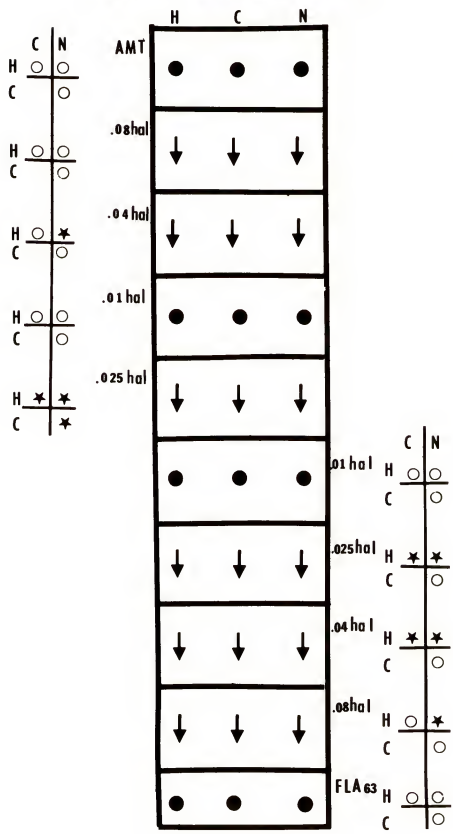
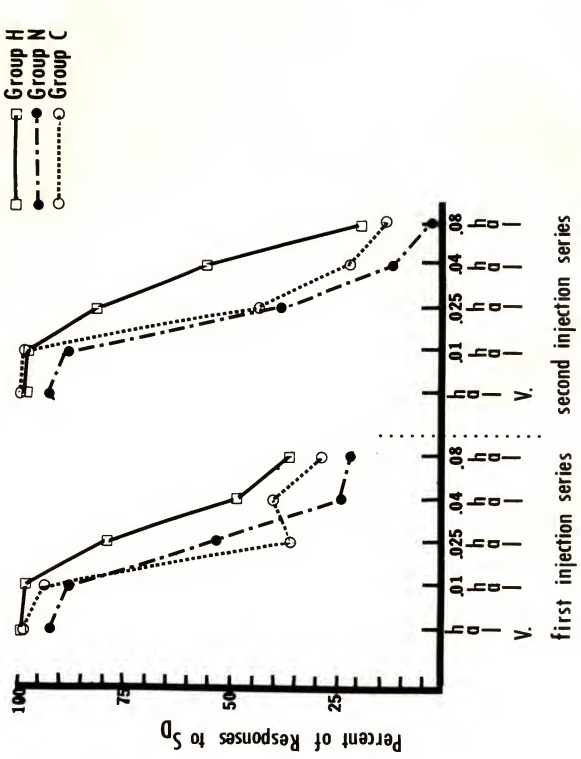

Percent of Responses During $S_D$
H
C
N
AMT
.08hal
.04 hal
.01 hal
.025 hal
.01 hal
.025hal
.04 hal
.08hal
FLA 63

Figure 7: Mean percent of responses during $S_D$ after administration of haloperidol.

hal = haloperidol-dose in mg/kg;
hal V. = haloperidol vehicle.


Group H
Group N
Group C
Percent of Responses to $S_D$
100
75
50
25
h a — V.
.01 h a —
.025 h a —
.04 h a —
.08 h a —
first injection series
second injection series

relationships were found for Group N that were similar to those of the first series. The dose-effect pattern of Group C response decreases was the same as that of Group N. During the ascending series the 0.08 mg/kg dose was more effective in decreasing responding for Group H than was the 0.04 mg/kg.

Comparisons between similar doses given during the descending and ascending series of haloperidol indicated that all of the second injections were more effective in decreasing the responses of Group N than were the first administrations. The second injections of 0.04 mg/kg and 0.08 mg/kg were more effective than their paired doses for decreasing Group C responses. The second 0.08 mg/kg injection was more effective than the first 0.08 mg/kg dose in decreasing responding during $S_D$ by Group H.

Percent correct. Prior to the administration of any drug agents (D 33 and D 34) and at all subsequent nondrug periods ND 1-13) and following vehicle injections, the percent correct scores of the animals in Group H were significantly lower than those obtained by Groups C and N (see Figure 8). At these times, the percent correct scores of Groups C and N were not significantly different from each other.

Figures 8 and 9 represent the changes in the percent correct scores after the administration of the various drugs. Haloperidol was the only agent that altered these scores in any of the groups. Since haloperidol was found to produce major decreases in responding during $S_D$ periods, it was possible that slight alterations in discrimination performance would be

Figure 8: Mean percent of correct responses in brightness discrimination task.

D = day; sal = saline; ND = nondrug session; hal V. = haloperidol vehicle; hal = haloperidol-dose in mg/kg; FLA V. = FLA 63 vehicle; nr = responses to less than 20 percent of stimulus presentations.

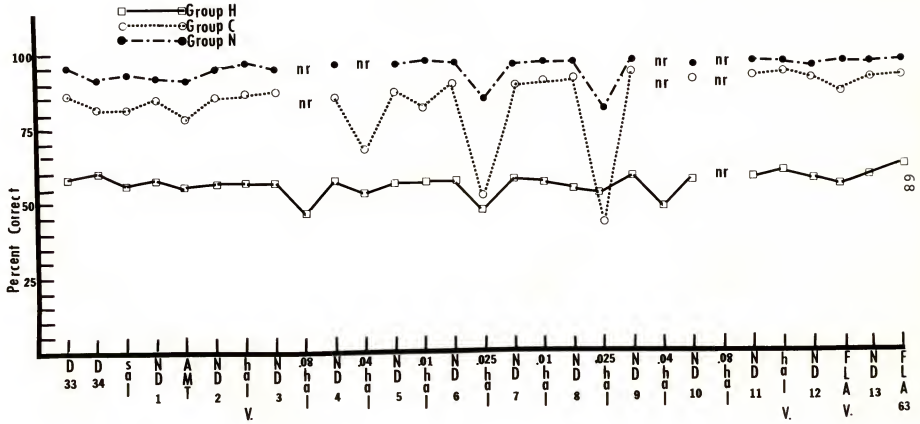
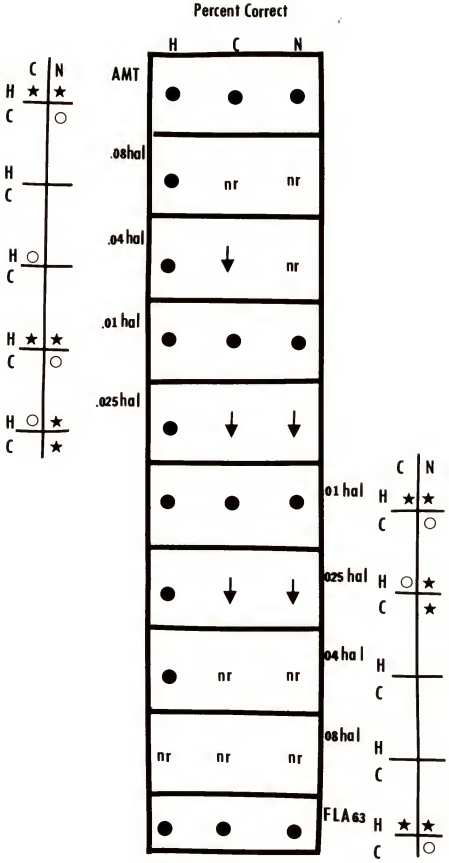

Group H
Group C
Group N
Percent Correct
100
75
50
25
nr
nr
nr

Figure 9: Changes in percent of correct responses after drug administrations.

hal = haloperidol-dose in mg/kg.
Center chart represents alterations within each group--filled circles = no change; arrows = decrease in responding; nr = responses to less than 20 percent of stimulus presentations.
Side figures indicate between group differences after drug administration.C=Group C; H = Group H; N = Group N.
Intersection of groups on grids adjacent to drugs indicates significant (star) or nonsignificant (open circle) group differences.


Percent Correct
H
C
N
AMT
.08hal
.04 hal
.01 hal
.025 hal
nr
FLA 63

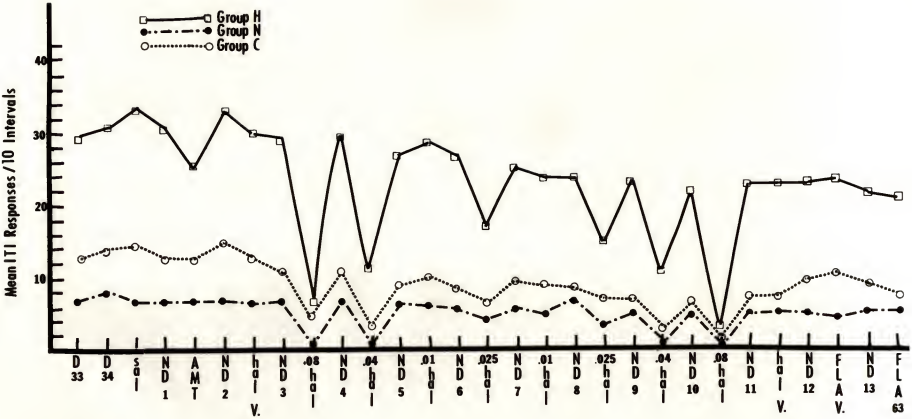
represented as large percentage changes. Under these circumstances, the meaning of the percent correct score as a measure of discriminative capacity becomes questionable. Therefore, it was decided not to consider drug-induced changes in percent correct scores unless the majority of the animals in a group were still responding to approximately 20 percent of the $S_D$ presentations.

Percent correct scores of Groups C and N decreased following several of the haloperidol injections. Scores of Group C were not different from those of Group H after the first 0.04 mg/kg dose and both 0.025 mg/kg doses of haloperidol. Since haloperidol-induced decreases in the percent correct scores of Group N after both 0.025 mg/kg injections were not as large as those of Group C, Group N remained superior to Group H. All effective haloperidol doses decreased the percent correct scores of Group N to a similar degree. The second administration of 0.025 mg/kg haloperidol produced the greatest disruption in the percent correct scores of Group C followed in order of decreasing disruption by the first 0.025 mg/kg, and the first 0.04 mg/kg injections. Group H percent correct scores were not affected by the drug administrations.

Intertrial interval (ITI) responses. On all of the vehicle and nondrug days prior to nondrug period 3 (ND 3) (see Figure 10), Group H responded significantly more during the first five ITI sec than did Group C which responded more than Group N. From ND 3 until the conclusion of the study, Group H responded more than Groups C and N which did not differ significantly from each other.

Figure 10: Mean intertrial interval responses per ten intervals in brightness discrimination task.

D = day; sal = saline; ND = nondrug session; hal V. = haloperidol vehicle; hal = haloperidol-dose in mg/kg; FLA V. = FLA 63 vehicle.


Group H
Group N
Group C
Mean ITI Responses/10 Intervals
40
30
20
10
D 33
D 34
sal
ND 1
AMT
ND 2
hal V.
ND 3
.08 hal
ND 4
.04 hal
ND 5
.01 hal
ND 6
.025 hal
ND 7
.01 hal
ND 8
.025 hal
ND 9
.04 hal
ND 10
.08 hal
ND 11
hal V.
ND 12
FLA V.
ND 13
FLA 63

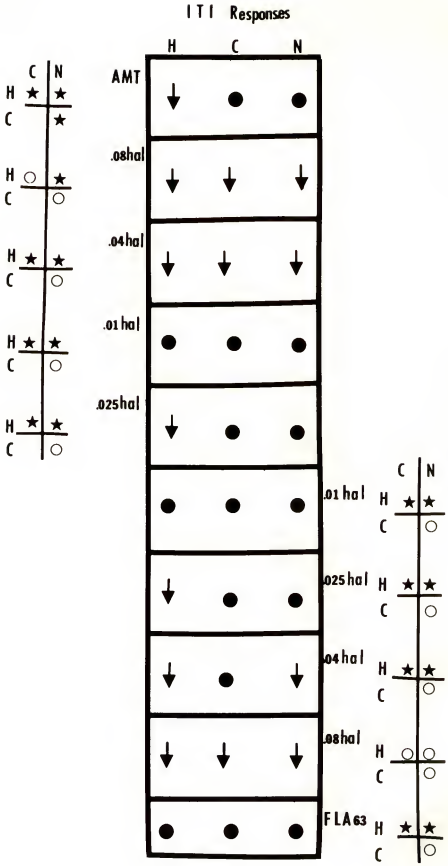
The effects of the various pharmacologic agents on ITI responses are illustrated in Figures 10 and 11. Significant decreases were found to occur in Group N ITI responses after administration of the 0.08 mg/kg and 0.04 mg/kg doses of haloperidol and in Group C ITI responses under the highest haloperidol dose and the first 0.04 mg/kg dose. AMT and all haloperidol doses with the exception of the lowest (0.01 mg/kg) significantly decreased the ITI responses of Group H but between-group differences were altered only after administration of the high dose of haloperidol. The difference between Groups C and H was eliminated after the first administration of the high dose. Following the second administration of 0.08 mg/kg, all group ITI response differences were eliminated.

ITI responses of Groups H and C on nondrug days fluctuated during the portion of the study analyzed. Group H responded more on the nondrug days prior to ND 5 than afterwards. On ND days, the greatest ITI responding by Group C was found prior to ND 3 while the least amount of ITI responding occurred during the second haloperidol series (ND 9, 10, 11). The number of ITI responses on all other nondrug days was intermediate between these high and low periods.

These ITI fluctuations make it difficult to compare the effects of the first and second series of haloperidol injections on the ITI responding of Group H or to include the first 0.025 mg/kg and 0.01 mg/kg injections in determining the dose-response curve of the first series. The higher doses of haloperidol administered during the stable ITI period prior to

Figure 11: Changes in intertrial interval responses after drug administrations.

hal = haloperidol-dose in mg/kg.
Center chart represents alterations within each group--filled circles = no change; arrows = decrease in responding.
Side figures indicate between group differences after drug administrations. C = Group C; H = Group H; N = Group N.
Intersection of groups on grids adjacent to drugs indicates significant (star) or nonsignificant (open circle) group differences.


ITI Responses
H
C
N
AMT
.08hal
.04hal
.01hal
.025hal
FLA63
C N
H ★ ★
C ★
H ○ ★
C ○
H ★ ★
C ○
H ★ ★
C ○
H ★ ★
C ○
.01hal
.025hal
.04hal
.08hal
FLA63

ND 5 did not differ from one another in producing decreases in ITI responding. Increasing doses in the second ascending series of injections resulted in progressively increasing effects on the ITI responses of Group H. Within Groups C and N, the effective haloperidol doses did not produce differential response decreases.

At the time of the expected effects of FLA 63 on central NE (4 hr after injection) none of the discrimination measures were altered in any of the groups. On the day following the administration of FLA 63, four animals in Group H, one in Group C and two normal rats became ill and died.

Observations. On completion of the haloperidol sessions, the rats were tested for catalepsy using a spool test (Aspen et al., 1973) and the latency to front paw withdrawal was recorded. The reaction of the rats to the rat chow given to them in their home cages was observed at the conclusion of the experimental sessions. The general behaviors of the animals prior to and at the conclusion of the sessions were noted.

Cataleptic responses were never observed in any of the rats; the animals removed their paws as soon as they were placed on the spools. All animals responded as usual to the rat pellets placed in their home cages and general behaviors before and after the experimental sessions were not different on drug or vehicle days.

Discussion

In agreement with previous reports (Woodruff and Isaacson, 1972), animals with damage to the hippocampus were impaired in performance of the operant simultaneous brightness discrimination. Although they pressed one of the two available response levers as frequently as controls during the presentation of the stimulus light ($S_D$), they pressed the correct lever directly under the $S_D$ significantly less than controls. In addition, they emitted significantly more nonreinforced intertrial interval (ITI) responses than did control animals. The number of ITI responses emitted by Group H was found to decrease during training but was always higher than the number of ITI responses emitted by the controls.

Blocking catecholamine synthesis with AMT significantly altered the discrimination performance of animals with damage to hippocampus but did not affect the performance of Groups C and N. The ITI responses of the animals with damage to the hippocampus decreased after the administration of AMT while all other performance measures were unchanged.

Haloperidol altered the performance of all of the animals. However, the drug effects were different among the experimental groups with respect to the discrimination measures affected, the threshold doses necessary to produce changes, and the magnitude of the behavioral changes. There were no differences among the groups in the threshold doses of haloperidol required to decrease the percentage of responses during the presentation of the light. However, in general, animals with damage to the hippocampus decreased responding less than did the other ani-

mals after the administration of an effective dose. The scores of Group C animals were intermediate between Groups H and N at several of the effective haloperidol doses. This suggests that animals of Group C were somewhat less affected than those of Group N.

There were cumulative effects of the drug. The second administration of the drug at various doses decreased responding during the presentation of the light more than did the first injection at the same dose. This occurred less frequently in Group H than in the other groups, suggesting that the animals with damage to the hippocampus had less of a cumulative effect. Thus, differences in both the magnitude of response to the drug during the presentation of the light and the apparent reduction in cumulative effects indicate that the haloperidol is less effective in animals with damage to the hippocampus.

The effects of haloperidol on the percentage of correct responding to $S_D$ were considered during the sessions in which the majority of the experimental animals responded to at least 20 percent of the $S_D$ presentations. Since haloperidol altered the responses during the $S_D$ in animals of Group H less than the responses of control animals, it was possible to examine the percent correct scores of Group H more frequently than those of the others. Haloperidol was found to decrease the baseline percent correct scores of the control animals but it did not aggravate the already impaired performance of animals with damage to the hippocampus. After the first 0.04 mg/kg and both 0.025 mg/kg doses of haloperidol, the discrimination performance of Group C declined to the level of Group H. While

the percent correct scores of the normal animals declined after the administration of both 0.025 mg/kg doses of haloperidol, these alterations were much less than those of Group C and the discrimination performance of Group N never approached the impaired performance of Group H. The percent correct scores of animals with damage to the hippocampus after haloperidol did not differ significantly from their performance during nondrug sessions.

Haloperidol administration was found to decrease the ITI responses of all animals. However, the threshold for haloperidol-induced response decreases was lower for animals with damage to the hippocampus than for the other animals. Only the highest doses of haloperidol significantly decreased the ITI responding of control animals while administration of all doses from 0.025 to 0.08 mg/kg decreased these responses in Group H. Although the drug-induced response decreases occured at lower dose levels in Group H, these animals continued to respond more than control animals until the highest doses were administered. At these times, the number of responses emitted were not significantly different from control levels.

A comparison of the drug effects in the individual groups suggests that different mechanisms may be responsible for the percent of responses during the light and for the ITI response rate. The percent of reinforced responses are more disrupted than are nonreinforced ITI responses in Groups C and N. The brightness discrimination, per se, may be associated with the percent responding to $S_D$ since both responses to $S_D$ and percent

correct responses decrease following haloperidol. Thus, both responding during the $S_D$ and successful performance appear to be related and require higher DA system activity than is available after haloperidol administration.

In Group H, the ITI responses are more susceptible to AMT than are the responses made in the presence of the light. This may indicate that different mechanisms are involved in these types of responses. The fact that the ITI responses decline during training while the responses to the light are unaltered further supports the concept of separate mechanisms. Still another mechanism may be involved in the use of the light in guiding performance but this mechanism does not appear to be available to animals in Group H. To summarize, three seperable components are involved in the discrimination performance: (1) responding in the presence of the light, (2) responding to the lever under the light, and (3) responding in the absence of the light. The first two appear to be closely linked in Groups C and N but dissociated in animals with hippocampal damage.

Since the discrimination performance as indicated by the percent correct measure suggests that the selection of the bar that is pressed by the control animals is under the control of the $S_D$ while the near random performance of Group H is not, the selective effect of haloperidol on the successful discrimination performance of Groups C and N may be due to the drug's action on mechanisms related to the sensory control of behavior leading to reinforcements. Decreases in the significance of stimuli have been attributed to neuroleptics such as haloperidol

(Key, 1961; Weiss and Laties, 1964). Damage to the neocortex enhances the haloperidol-induced disruption of the discrimination performance.

The findings described above show that the ability to perform the brightness discrimination, per se, is compromised by blocking DA activities or by the removal of the hippocampus. This suggests that damage to the hippocampus reduces the effectiveness of some system that is also regulated in part by DA and that is critical for the brightness discrimination problem.

If the efficiency of this system has been reduced by hippocampal destruction then the enhancement of the activity of the DA system might reverse the impairment. Accordingly, the effect of the administration of amphetamine, L-DOPA, or selective DA receptor stimulants (e.g., apomorphine or ET-495) to animals with damage to the hippocampus should be investigated. Amphetamine has been reported to facilitate performance of intact animals on a brightness discrimination (Rahmann, 1970) although there are reports of amphetamine-induced brightness discrimination impairments (Beckwith et al., 1974). The results of the present study suggest that increases in catecholaminergic activities might be beneficial to the operant brightness discrimination performance of animals with damage to the hippocampus.

Since blocking DA decreases the percentage of responding during the presentation of the stimulus in all animals, DA may

exert a regulatory influence on the mechanisms underlying these responses. Although the baseline responses during the presentation of the light are similar among the groups, the responses of control animals are dictated by the position of the light while Group H responses are not. Thus, different mechanisms may be involved in responding during the presentations of the light in Group H as compared with the controls. Since more DA blocking is necessary to decrease the former responses in Group H and also since this group shows less cumulative effects of the drug, the responses in the presence of the light are likely to be the result of a greater effectiveness of the DA system on the mechanism involved.

Responses during the ITI component of the discrimination task are greater in Group H and are selectively affected by AMT and by 0.025 mg/kg of haloperidol in comparison to control animals. It is possible that high response rates are particularly sensitive to response decreasing effects of the drug agents. Since high doses of haloperidol lowered the high numbers of ITI responses made by animals in Group H to control levels, the high level of ITI responding by Group H may be the result of a highly active DA system. The fact that AMT, but not FLA 63 was found to decrease these responses of Group H suggests that blocking of DA synthesis rather than NE synthesis by AMT was responsible for its actions on the ITI responses of Group H.

Several factors suggest that a highly active DA system associated with the ITI responses of Group H is not the same

as that responsible for the responses in the presence of the stimulus light. AMT was able to selectively decrease the ITI responses, and these responses decreased during the course of training, while the responses in the presence of the light did not.

The above analysis indicates that different DA activities can be involved in the different components of the discrimination task. For example, high DA activity appears to be associated with the ITI and $S_D$-based responses of Group H while low DA activity may be involved in the deficient performance of the brightness discrimination, per se. There are several major DA projection systems and it is possible that DA activities in different parts of the systems are affected in opposite directions following damage to the hippocampus. This presents problems in any attempt to reverse the different impairments of animals with damage to the hippocampus found in the operant brightness discrimination task. While the inappropriate ITI responses can be reduced by blocking DA activity, it appears that facilitation of this activity may be necessary for improvements in the ability to discriminate, per se.

Since catalepsy was not found to result from haloperidol and the reaction of the animals to the food pellets given to them in their home cages at the conclusion of an experimental session and the general behaviors of the animals outside of the operant box were unaffected by the drug, the virtual elimination of barpressing found at high doses of haloperidol may be related to specific processes involved in the operant task.

At present, it is not possible to determine the nature of the effects of the high doses of haloperidol on these processes.

The failure to find performance effects after blocking NE suggests that NE may not be directly involved in the performance of the brightness discrimination problem. On the other hand, synthesis inhibition may have been incomplete or mobilization of"reserve"pools of NE may have occurred. The toxic and the lethal effects of FLA 63 on the day following its supposed effects on central NE are similar to those described in the discussion of the DRL task. The dose administered was higher in the present task and a greater proportion of the animals died than in the previous study. The reasons for these effects after FLA 63 are unknown but indicate that this agent should be used with caution in animals involved in extensive behavioral testing.

## GENERAL DISCUSSION

The present series of investigations were undertaken in order to obtain information concerning possible changes in activities of central catecholamine systems subsequent to bilateral hippocampal damage. As described in the introduction, agents which enhance catecholaminergic effectiveness produce behaviors in intact animals which resemble behaviors of animals with hippocampal damage. This suggests that, in the intact animal, the hippocampus and catecholamine systems might exert influences that are antagonistic to one another. Damage to the hippocampus might therefore increase the effectiveness of catecholamine systems. If this were so, drugs which increase catecholamine activities might be expected to have greater than normal effects in animals with hippocampal damage and agents which block catecholamines might produce reduced effects in the brain-damaged animals. If enhanced effectiveness of the catecholamine systems were responsible for some of the behavioral impairments following damage to the hippocampus, blocking catecholamine activities might reverse the impairments.

The results of the present experiments support these predictions. High doses of amphetamine produced greater decreases in response rates on an FR schedule in animals with hippocampal damage than in control animals. These decreases were associated with the appearance of stereotyped behaviors and this sug-

gests that the lesion may have altered the effectiveness of the DA system. Blocking DA receptors with haloperidol improved the deficient DRL performance of the animals with damage to the hippocampus and more haloperidol was necessary to eliminate lever pressing in these animals than in control animals. Haloperidol was found to decrease the inappropriate ITI responses in the animals performing on the operant brightness discrimination task. In addition, the same drug was less effective in blocking the responses made by the brain-damaged animals in the presence of the light than it was in control animals.

These results suggested that damage to hippocampus enhanced the effectiveness of the DA systems in the guidance of behavior. Several alterations in the DA systems might occur if removal of hippocampus eliminated a direct inhibition on these systems. Increases in the activity of DA systems might occur through changes in the levels, rate of synthesis, amount or rate of release, reuptake, and/or metabolism of DA. In principle, these changes could be detected by the use of fluorimetric, radioisotopic, chromatographic, histochemical fluorescent, autoradiographic and push-pull cannulae techniques. Electrophysiologically, it might be expected that stimulation of the DA neuronal systems would result in enhanced effects on postsynaptic single unit discharges. Electron micrographic studies might detect alterations in the synaptic vesicles associated with the changes in the biochemical indices. Increases in presynaptic activities might lower the sensitivities of postsynaptic receptors. This could be detected by the ionto-

phoresis of receptor stimulants to postsynaptic sites.

Another mechanism could account for the apparent enhancement of the effectiveness of the DA systems following hippocampal damage. Both the hippocampus and DA systems might converge on a third neural system. If the hippocampus and DA systems were antagonistic with respect to the output of the third system, removal of the hippocampus would result in an increase in the effectiveness of the DA systems on this third system. The hippocampal input to the third system could be mediated through mono- or poly-synaptic connections.

If a balance between the DA systems and the hippocampus on some third system was disrupted by hippocampal damage, behavioral alterations could be identical to those occurring if direct hippocampal inhibition on DA systems was removed. However, since the activity of the DA system in the balance model need not be affected by hippocampal removal, biochemical changes in the DA system might not accompany hippocampal removal. However, both electrophysiological stimulation and administration of agents which enhance catecholaminergic activity should have greater than normal effects on the output of the third system. Receptor-blocking agents should have diminished effects.

If the hippocampus and DA neurons converge on a third system, then the removal or reduction of the hippocampal input might result in collateral sprouting of the DA axons to the partially denervated cells. If this were the case, and if these collaterals were functional, an increased influence of

the DA system would be expected. Collateral sprouting of DA axons would lead to increases in the biochemical indices reflecting catecholamine activities. The axon sprouts could be detected by histofluorescence, electronmicroscopy, and autoradiography. These morphological changes would not be expected to occur from direct removal of hippocampal inhibition of a catecholamine system.

An unexpected finding in the behavioral studies was that in the case of the brightness discrimination, per se, hippocampal damage and decrease of DA activity had the same effect. Two possibilities exist for the mechanism underlying the similar effect of DA receptor blockade and hippocampal damage. If the hippocampus mono- or poly-synaptically exerted an excitatory influence on a DA system, removal of the hippocampus would decrease the effectiveness of that system. If both hippocampus and a DA system acted on yet a third system in a similar manner, removal of either input would compromise the activities of the third system. The changes expected to occur in the former case would be opposite to those detailed above where the hippocampus usually exerted an inhibitory influence on DA systems. If the hippocampus and the DA systems exerted similar effects on a third system, removal of one of the former would result in decreases in the stimulating and increases in the blocking properties of electrical and chemical stimuli on the output of the third system. Collateral sprouting, if functional, would not be expected here. If it did, the deficit might not occur.

The above findings indicate that the behavioral deficiencies found in animals with hippocampal damage may result from alterations in mechanisms which are regulated in part by DA and that the alterations may be in different directions. If this were to be the case it would preclude the possibility of any single, global therapies for the behavioral impairments of the brain-damaged animals. However, since there are many DA systems in the brain, the possibility that a brain lesion would alter some of these systems in different directions is not surprising. The major DA projection systems include the nigrostriatal DA system with its cell bodies in the substantia nigra and terminal projections in the caudate-putamen (Ungerstedt, 1971a; Lindvall and Björklund, 1974); the mesolimbic DA system with cell bodies located dorsally and laterally to the interpeduncular nucleus and terminal projections in the nucleus accumbens septi, nucleus interstitial stria terminalis, and olfactory tubercle and nucleus amygdaloideus centralis (Ungerstedt, 1971a; Lindvall and Björklund, 1974); and the hypothalamic DA system with cell bodies in A12 of the hypothalamus and projections to the median eminence (Ungerstedt, 1971a). DA has also been found in the neocortex, septal area, piriform cortex, cingulate cortex, entorhinal cortex, and hippocampus (Thierry, Blanc, Sobel, Stinus, and Glowinski, 1973; Brownstein, Saavedra, and Palkovits, 1974; Fuxe, Hökfelt, Johansson, Jonsson, Lidbrink, and Ljungdahl, 1974; Koslow, Racagni, and Costa, 1974; Lindvall and Björklund, 1974; Lindvall, Björklund, Moore, and Stenevi, 1974; Lindvall, 1975).

Of the above structures, the hippocampus projects directly to the septal area, nucleus accumbens septi and entorhinal cortex (Raisman, Cowan, and Powell, 1966; Swanson and Cowan, 1975) but there is no reason to believe that alterations in the effectiveness of the catecholamine systems should take place only, if at all, in these areas. The influence of hippocampal damage could be mediated via a poly-synaptic network to any of these DA-containing structures.Future investigations should attempt to discover the critical loci of the systems which contain DA and which are altered following damage to the hippocampus. The mesolimbic and nigrostriatal dopaminergic systems involved in amphetamine-induced stereotyped behaviors (see FR discussion) are also implicated in the actions of neuroleptics such as haloperidol (Costall et al., 1975; Costall and Naylor, 1974c). These structures may therefore be critically involved in the catecholaminergic alterations associated with damage to the hippocampus. Both the location of the critical loci and the nature of the alterations should be investigated.

After damage to the hippocampus the cannulation of DA receptor blockers into various DA-containing structures should be studied in animals performing on the DRL and brightness discrimination tasks in order to determine the areas affected by haloperidol in the present studies. If systemic administration of agents that enhance DA functioning are able to reverse the brightness discrimination, per se, deficit of the brain-damaged

animal, the critical DA areas involved should be determined by the cannulation of agents which enhance DA into various DA-containing structures.

The specific relationship of the alterations in the DA systems after hippocampal damage to the behaviors of the animals needs to be studied. It may be possible to mimic these behaviors in intact animals by the administration of the appropriate agents into appropriate sites. It may be possible to prevent the neurochemical changes from occurring subsequent to hippocampal damage and to reverse the behavioral changes which do occur. Baisden (1973) was able to ameliorate, in part, the DRL deficit and the passive avoidance impairment of animals by intraseptal injection of 6-hydroxydopamine prior to hippocampal damage. Although he attributed his findings to destruction of the NE terminals in the septal area, the effects might have been due to changes in DA terminations. If the critical DA areas and alterations affected by hippocampal damage were discovered, it might be possible to develop agents with specific affinities for the critical loci and with the appropriate actions there. Various combinations of such agents might make systemic administrations feasible for therapeutic purposes.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Robert L. Isaacson, Chairman
Professor of Psychology

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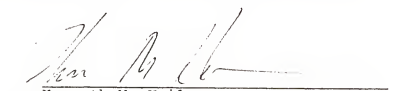
I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



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